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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Accompanying Application

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Entry into National Phase of International Application No.:

PCT/GB01/02541 under 35 U.S.C. § 371

For : SERINE PROTEASE INHIBITORS

Docket No. : 00220US

PRELIMINARY AMENDMENT ON FILING

Attention: DO/EO

Box PCT

Assistant Commissioner for Patents

Washington, DC 20231

Sir:

Before calculating the filing fee, please amend the accompanying application as follows:

Please add the Abstract attached on a separate sheet.

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In the Description

At page 8, line 21, page 9, line 11 and page 9, line 14, please replace the term "L-Lp(D)<sub>n</sub>" with the term "L-Lp(D)<sub>n</sub>".

In the Claims

Please cancel Claims 17, 18, 26, 27, 28 and 30 (without prejudice); enter the indicated amendments to Claims 2 to 11, 13 to 16, 19 to 22, 24 and 25; and enter new Claims 31 to 35. Directions for amendment of claims are indicated on the copy of the attached hand amended ("marked up") original claims, showing in manuscript the amendments that have been made and the origins of the new claims. Clean forms of new and rewritten claims are included in the attached "Clean Set of Claims" document.

Remarks

This application seeks protection for certain novel compounds that are inhibitors of the serine protease, Factor Xa, and are useful for the treatment of thrombotic disorders. It is the national stage of an international application, the claims of which were drafted in accordance with international practice.

Applicants now wish to amend the application to bring it into conformity with United States patent practice.

For the assistance of the Examiner, a copy of the original claims is attached, as noted above, showing in manuscript the amendments that have been made.

The description at pages 8 and 9 has been brought into conformity with claims 4 and 5 as originally filed.

Claims 17, 18, 26, 27, 28 and 30 have been cancelled, without prejudice.

Claims 2 to 11, 13, 15 to 16, 19 to 22, 24 and 25 have been rewritten in single dependent form.

Claim 14 now depends from any one of claims 1 to 13, 15 to 16 and 19 to 22. Claim 24 now depends from claim 14.

New claim 31 is based upon a combination of original claims 1, 11, 13, 14, 24 and 21. It is noted that all of the original claims were drafted in multiple dependent form, and hence new claim 31 is fully based on these original claims.

New claim 32 is based upon new claim 31, and additionally incorporates the subject matter of Claims 12, 22 and 8.

New claim 33 is based upon claims 2, 13, 14 and 24 and additionally incorporates the preferred definition of  $R_2$  at page 20, line 16 to page 21, line 29, and the preferred definition of Cy at page 13, lines 13 to 21.

New claim 34 is based upon new claim 33 and claim 4.

New claim 35 is based upon new claim 33 and claim 5.

Favorable consideration of the application is requested.

Respectfully submitted,



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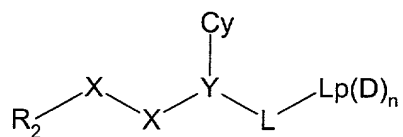
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February 1, 2002

Attachments: Abstract on separate sheet  
Hand-amended (marked-up) Claims  
Clean Pending Claims

## A B S T R A C T

Compounds of formula (I)



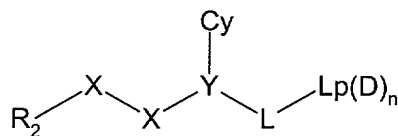
(I)

in which  $\text{R}_2$ , X, Y, Cy, L and  $\text{Lp(D)}_n$  have the meanings given in the specification, are inhibitors of the serine protease,

Factor Xa and are useful in the treatment of cardiovascular  
10 disorders.

Clean Set of Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

$\text{R}_2$  is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,  $\text{MeSO}_2$ - or  $\text{R}_1$ , or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or  $\text{R}_{1j}$ , and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that  $\text{R}_2$  cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO,  $\text{CR}_{1a}$ ,  $\text{C(R}_{1a})_2$  or  $\text{NR}_{1a}$  group, at least one X being C, CO,  $\text{CR}_{1a}$  or  $\text{C(R}_{1a})_2$ ;

each  $\text{R}_{1a}$  independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$\text{R}_1$  is as defined for  $\text{R}_{1a}$ , provided that  $\text{R}_1$  is not unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a  $CR_{1b}$  group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups  $R_{3a}$  or  $R_{3i}X_i$ ;

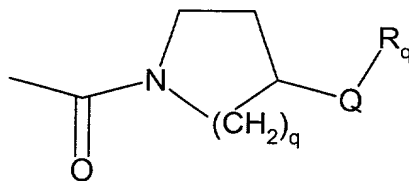
5 each  $R_{3a}$  independently is  $R_{1c}$ , amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkylloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a  
10 group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S; and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or  $-OCH_2O-$  which is bonded to two adjacent  
15 ring atoms in Cy;

$X_i$  is a bond, O, NH or  $CH_2$ ;

$R_{3i}$  is phenyl, pyridyl or pyrimidinyl optionally substituted by  $R_{3a}$ ; and

$R_{1b}$ ,  $R_{1c}$  and  $R_{1j}$  are as defined for  $R_{1a}$ ,

20 and  $-L-Lp(D)_n$  is of the formula:



wherein:

q is 1 or 2;

Q is  $-O-$  or  $-NH-$ ;

25 and  $R_q$  is  $R_c$  which is pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl or phenyl (which phenyl or pyridyl group may bear a fluoro, chloro, alkyl,  $CONH_2$ ,  $SO_2NH_2$ , dialkylaminosulphonyl, methoxy, methylthio, alkylsulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino,  
30 alkoxycarbonyl, acetyl amino, cyano, ethoxy, nitro, hydroxy,

alkylsulphonylamino, triazolyl or tetrazolyl substituent);  
or a physiologically-tolerable salt thereof.

2. (amended) A serine protease inhibitor compound according  
5 to Claim 1  
wherein:

$R_2$  is a 5 or 6 membered aromatic carbon ring optionally  
interrupted by a nitrogen, oxygen or sulphur ring atom,  
optionally being substituted in the 3 and/or 4 position (in  
10 relation to the point of attachment of X-X) by halo, nitro,  
thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano,  
haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or  
difluoromethoxy, carboxy, acyloxy,  $MeSO_2-$  or  $R_1$ , or the  
substituents at the 3 and 4 positions taken together form a  
15 fused ring which is a 5 or 6 membered carbocyclic or  
heterocyclic ring optionally substituted by halo, haloalkoxy,  
haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl,  
alkynyl or  $R_{1j}$ , and optionally substituted in the position  
alpha to the X-X group (i.e. 6 position for a six membered  
20 aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy,  
alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio  
with the proviso that  $R_2$  cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO,  
 $CR_{1a}$ ,  $C(R_{1a})_2$  or  $NR_{1a}$  group, at least one X being C, CO,  $CR_{1a}$   
25 or  $C(R_{1a})_2$ ;

each  $R_{1a}$  independently represents hydrogen, hydroxyl,  
alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl,  
alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino,  
acyloxymethoxycarbonyl or alkylamino optionally substituted by  
30 hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$R_1$  is as defined for  $R_{1a}$ , provided that  $R_1$  is not  
unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a  $CR_{1b}$  group;

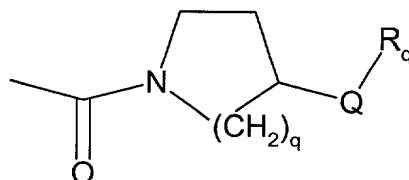
Cy is a saturated or unsaturated, mono or poly cyclic,



homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups  $R_{3a}$  or phenyl optionally substituted by  $R_{3a}$ ;

each  $R_{3a}$  independently is  $R_{1c}$ , amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

$R_{1b}$ ,  $R_{1c}$  and  $R_{1j}$  are as defined for  $R_{1a}$ , and  $-L-Lp(D)_n$  is of the formula:



wherein:

$q$  is 1 or 2;

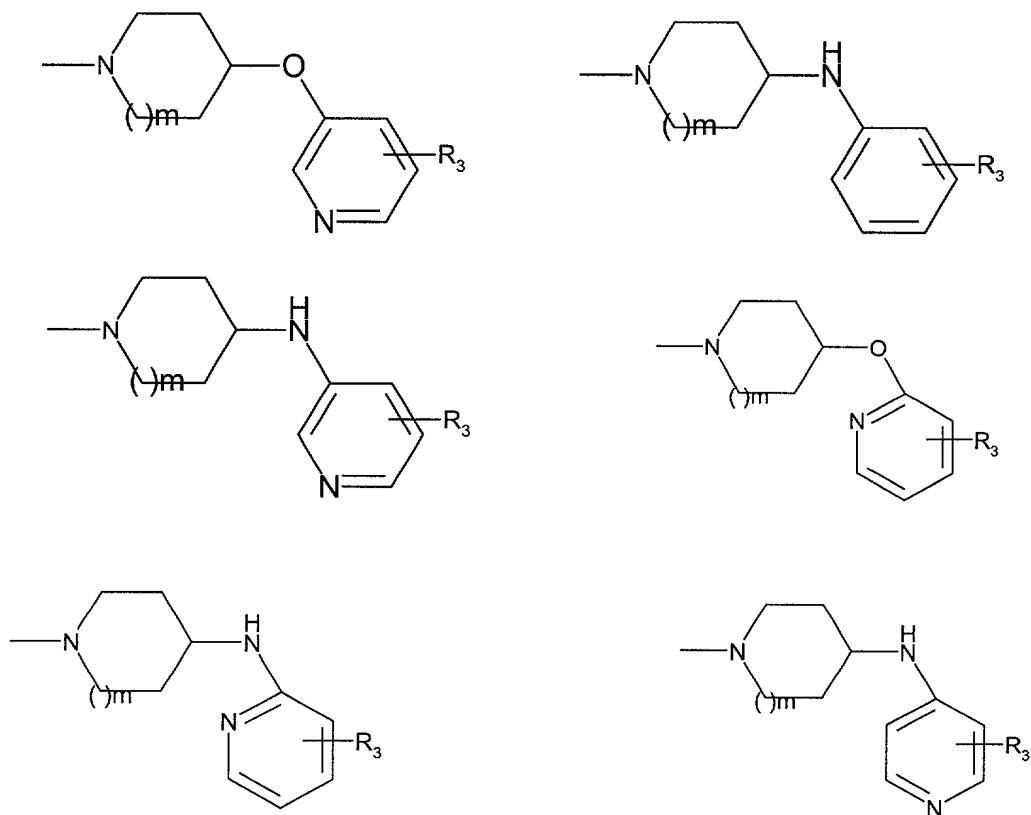
$Q$  is  $-O-$  or  $-NH-$ ;

and  $R_q$  is  $R_c$  which is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl,  $CONH_2$ ,  $SO_2NH_2$ , methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent);

or a physiologically-tolerable salt thereof.

3. (amended) A compound according to claim 1 wherein  $q$  is 2.

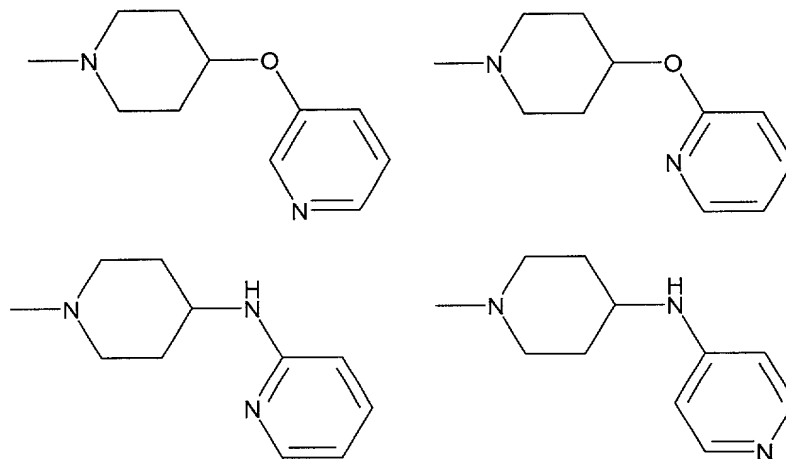
4. (amended) A compound according to claim 2 wherein  $-Lp(D)_n$  is selected from the following formulae:



wherein:

when R<sub>3</sub> is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxy, carbonyl, acetyl, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

The image displays two chemical structures. The structure on the left is 1-methyl-4-(pyridin-2-ylamino)piperidine, which consists of a piperidine ring with a methyl group on the nitrogen and a 2-pyridylamino group at the 4-position. The structure on the right is 1-methyl-4-(pyridin-2-yloxy)piperidine, which consists of a piperidine ring with a methyl group on the nitrogen and a 2-pyridyloxy group at the 4-position.



6.(amended) A compound according to claim 1 wherein Q is -NH-.

7.(amended) A compound according claim 1 wherein R<sub>c</sub> is pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimid-4-yl or phenyl.

8. (amended) A compound according to claim 1 wherein R<sub>c</sub> is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

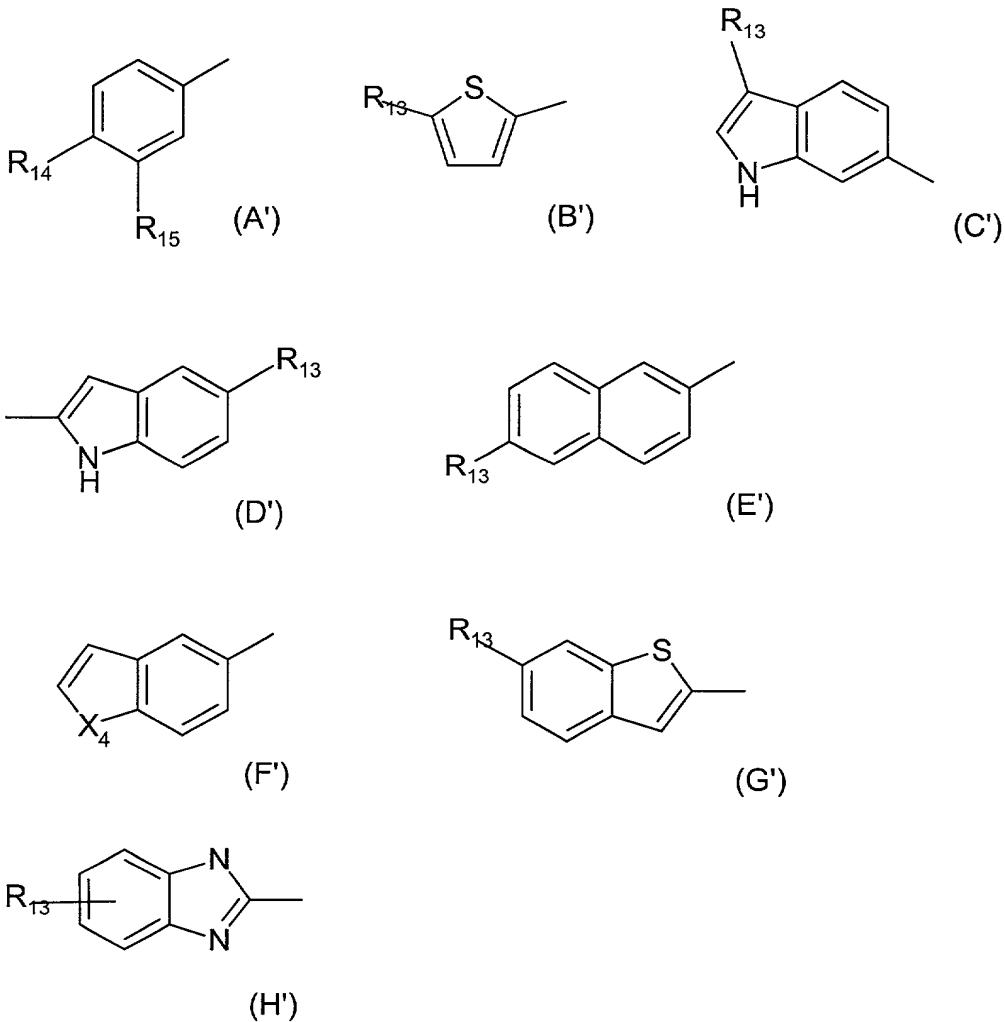
9. (amended) A compound according to claim 1 wherein R<sub>2</sub> is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

10. (amended) A compound according to claim 1 wherein optional substituents for R<sub>2</sub> are selected from:

fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetyl amino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido (CONH<sub>2</sub>),

aminomethyl, methoxy and ethoxy.

11.(amended) A compound according to claim 1 wherein  $R_2$  is selected from one of the formula (A') to (H'):



wherein  $X_4$  is O or S,  $R_{13}$  is selected from hydrogen, chloro or methyl and  $R_{14}$  is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and  $R_{15}$  is selected from  
 10 hydrogen, methyl, fluoro, chloro and amino.

12. A compound according to claim 11, wherein  $R_2$  is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

13. (amended) A compound according to claim 1 wherein -X-X- is -CONH-.

5 14. (amended) A compound according to any one of claims 1 to 13, 15 to 16 and 19 to 22 wherein Y is CH.

15. (amended) A compound according to claim 1 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl,  
10 thiazolyl, naphthyl, piperidiny, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by R<sub>3i</sub>X<sub>i</sub> in  
15 which X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub> and R<sub>3i</sub> is phenyl or pyridyl optionally substituted by R<sub>3a</sub>.

16. (amended) A compound according to claim 2, wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl,  
20 thiazolyl, naphthyl, piperidiny or cycloalkyl group.

17. (cancelled on national phase entry)

18. (cancelled on national phase entry)

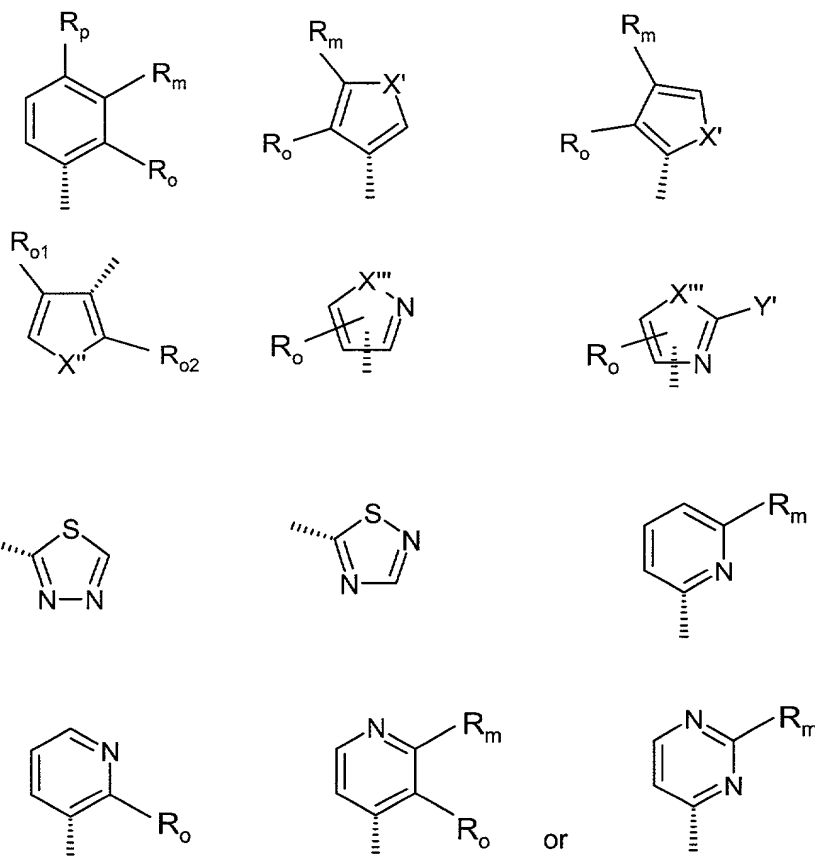
25

19. (amended) A compound according to claim 1 wherein R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl,  
30 methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl,

methysulphonylamido, ethylsulphonylamido,  
methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl,  
trifluoromethoxy, trifluoromethyl, bromo, pyrrolidin-1-  
ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and  
5 -OCH<sub>2</sub>O- (which is bonded to two adjacent ring atoms in Cy).

20. (amended) A compound according to claim 2 wherein R<sub>3a</sub> is  
selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl,  
ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl,  
10 carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl,  
methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,  
CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetylamino, methoxycarbonylamino,  
ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro,  
chloro, cyano, nitro, thiol, methylthio, methysulphonyl,  
15 ethylsulphonyl, methylsulphenyl, methylsulphonylamido,  
ethylsulphonylamido, methylaminosulphonyl,  
ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and  
trifluoromethyl.

20 21. (amended) A compound according to claim 1 wherein Cy is  
selected from:



wherein:

X' is selected from O, S and NMe;

5 X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R<sub>o</sub> is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and

10 methylsulphonyl;

R<sub>m</sub> is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S, and R<sup>11</sup> and R<sup>12</sup>

15 are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R<sub>p</sub> is selected from hydrogen and fluoro; or

$R_O$  and  $R_m$  or  $R_m$  and  $R_p$  form an  $-OCH_2O-$  group; or  
 $R_O$  and  $R_m$  together with the ring to which they are attached  
form a 5 or 6 membered aryl or heteroaryl ring (wherein the  
heteroaryl ring contains 1 or 2 heteroatoms selected from  
5 nitrogen, oxygen and sulfur); and  
one of  $R_{O1}$  and  $R_{O2}$  is hydrogen and the other is  $R_O$ .

22. (amended) A compound according to claim 1 wherein Cy is  
selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl,  
10 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-  
2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl,  
thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-  
yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-  
4-yl, quinolin-5-yl and quinolin-8-yl.

15

23. A compound as claimed in Claim 1, which is selected from  
1-(indol-6-carbonyl-D-phenylglyciny)l)-4-(4-pyridoxy)-  
piperidine; 1-[indole-6-carbonyl-D,L-(2-  
chlorophenyl)glyciny]l)-4-(pyridin-4-yloxy)piperidine, and  
20 physiologically-tolerable salts thereof.

24. (amended) A compound as claimed in Claim 14, in which the  
alpha atom in Y is carbon and has the conformation that would  
result from construction from a D- $\alpha$ -aminoacid  $NH_2-CR_{1b}(Cy)-$   
25  $COOH$  where the  $NH_2$  represents part of X-X.

25. (amended) A pharmaceutical composition, which comprises a  
compound as claimed in Claim 1 together with at least one  
pharmaceutically acceptable carrier or excipient.

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26. (cancelled on national phase entry).

27. (cancelled on national phase entry)

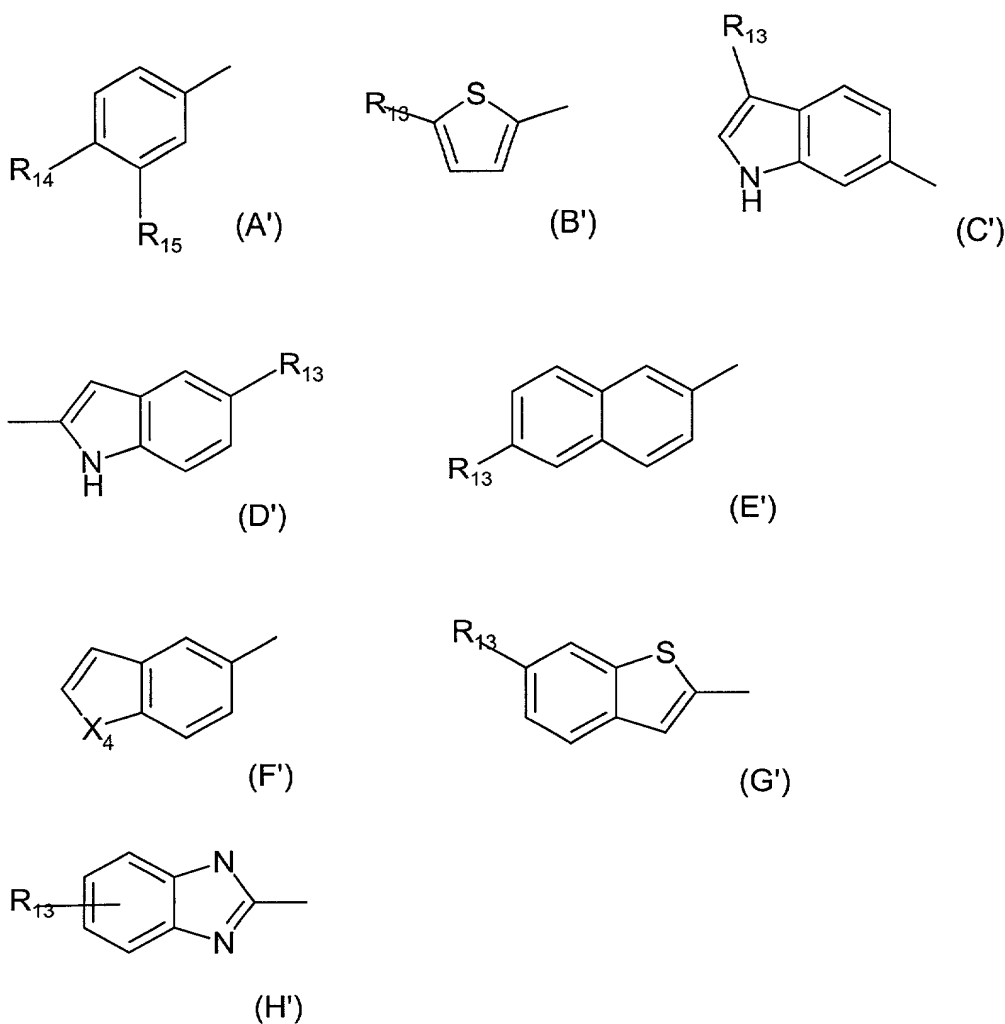


28. (cancelled on national phase entry).

29. A method of treatment of the human or non-human animal body to combat a thrombotic disorder, said method comprising  
5 administering to said body an effective amount of a compound according to Claim 1.

30. (cancelled on national phase entry).

10 31. (new) A compound as claimed in Claim 1, in which  $R_2$  is selected from one of the formula (A') to (H'):



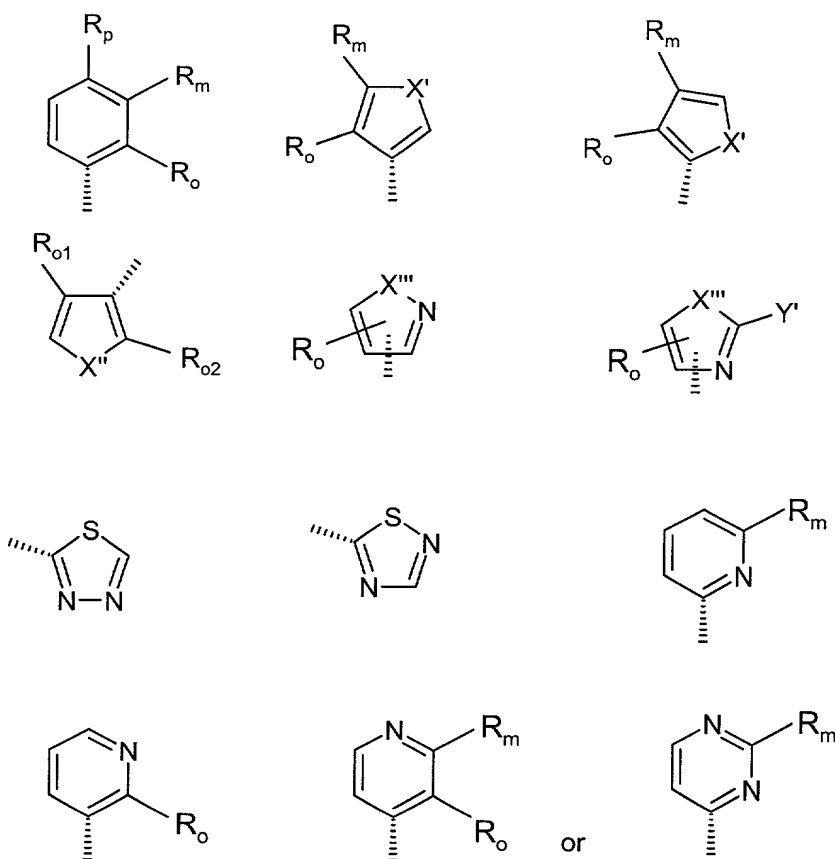
wherein  $X_4$  is O or S,  $R_{13}$  is selected from hydrogen,  
15 chloro or methyl and  $R_{14}$  is selected from hydrogen, methyl,

ethyl, fluoro, chloro, and methoxy and  $R_{15}$  is selected from hydrogen, methyl, fluoro, chloro and amino;

-X-X- is -CONH-;

Y is CH and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $NH_2-CR_{1b}(Cy)-COOH$  where the  $NH_2$  represents part of X-X; and

Cy is selected from:



10

wherein:

$X'$  is selected from O, S and NMe;

$X''$  is selected from O and S;

$X'''$  is selected from O, S, NH and NMe;

15  $Y'$  is selected from hydrogen, amino and methyl;

$R_o$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and

methylsulphonyl;

$R_m$  is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S, and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

$R_p$  is selected from hydrogen and fluoro; or

$R_O$  and  $R_m$  or  $R_m$  and  $R_p$  form an  $-OCH_2O-$  group; or

$R_O$  and  $R_m$  together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and

one of  $R_{O1}$  and  $R_{O2}$  is hydrogen and the other is  $R_O$ .

32. (new) A compound according to Claim 31, in which

$R_2$  is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl;

$Cy$  is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl; and

$R_C$  is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

33. (new) A compound according to Claim 2, in which

$R_2$  represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro,

difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, MeSO<sub>2</sub>-, hydroxy, methoxy, ethoxy, methyl, methoxycarbonyl, methylamino, ethylamino or amido, and optionally substituted  
5 at the 6 position by amino, hydroxy, fluoro, methoxycarbonyl, cyano or aminomethyl;

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

10 (iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally  
15 substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

20 (vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position  
25 by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

(xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position  
30 by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

(xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

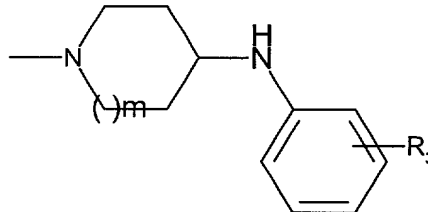
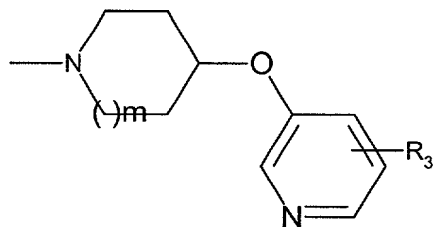
(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy;

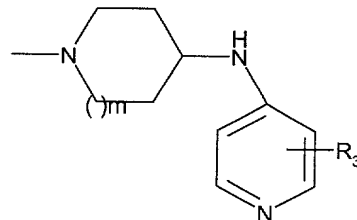
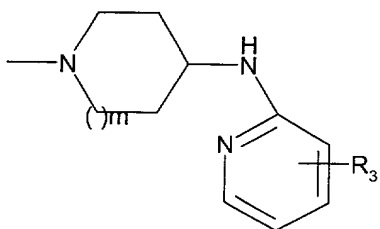
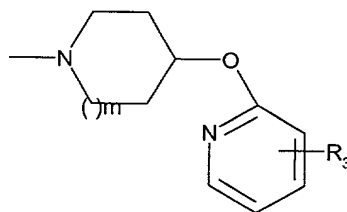
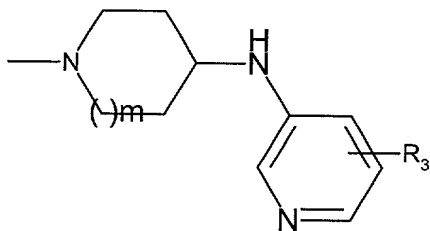
-X-X- is -CONH-;

Y is CH and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $\text{NH}_2\text{-CR}_{1b}(\text{Cy})\text{-COOH}$  where the  $\text{NH}_2$  represents part of X-X; and

Cy is selected from phenyl, 4-aminophenyl, 4-amidophenyl, 4-(N-methyl)amidophenyl, 4-(N,N-dimethyl)amidophenyl, 2-chlorophenyl, 2-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-carboxyphenyl, 3-ethylsulphonylaminophenyl, thien-2-yl, thien-3-yl, thiazol-4-yl, thiazol-5-yl, 2-methylthiazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, cyclohexyl and naphth-1-yl.

34. (new) A compound according to Claim 33, in which -Lp(D)n is selected from the following formulae:





5 wherein:

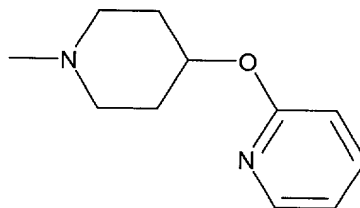
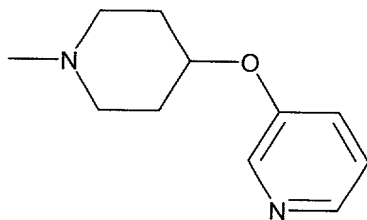
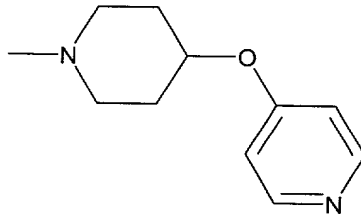
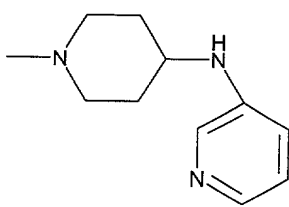
m represents 0 or 1; and

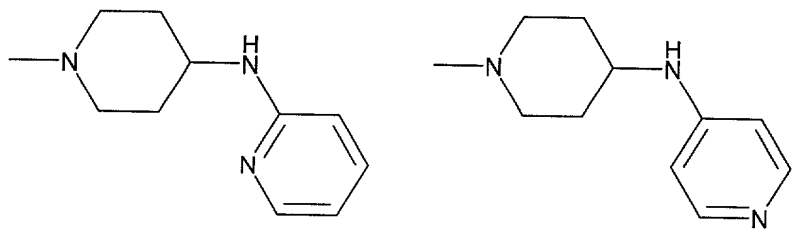
when  $R_3$  is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido,

10 alkoxycarbonyl, acetyl amino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

35. (new) A compound according to Claim 33, in which

15 -Lp(D)n is selected from the following formulae:





and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C<sub>1-6</sub> or C<sub>1-3</sub>; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 16 ring atoms.

- 5 Examples of particular values for R<sub>1a</sub> are: hydrogen, methyl or ethyl. R<sub>1a</sub> is preferably a hydrogen atom.

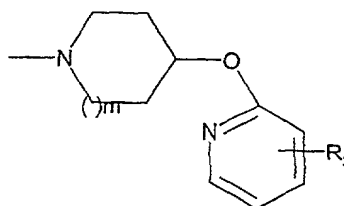
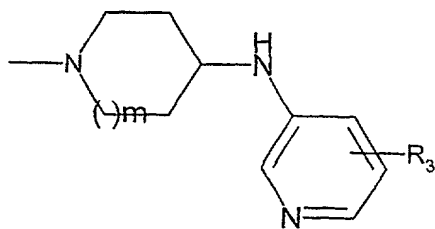
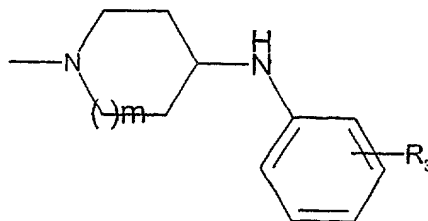
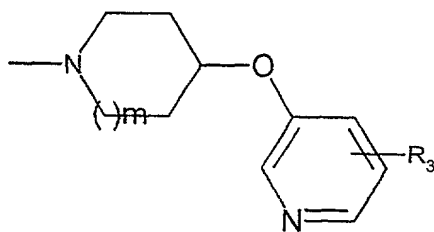
The linker group from the R<sub>2</sub> group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -CONR<sub>1a</sub>-, -NH-CO-, -NH-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-, -CH<sub>2</sub>O-, -OCH<sub>2</sub>-, -COO-, -OC=O- and

- 10 -CH<sub>2</sub>CH<sub>2</sub>-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH<sub>2</sub> or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-. In an alternative embodiment  
15 the linker is preferably a -OCH<sub>2</sub>- group.

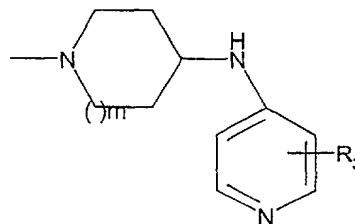
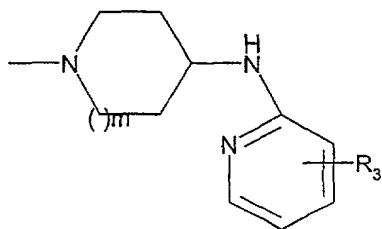
Examples of particular values for R<sub>1b</sub> are: hydrogen, (1-4C)alkyl, such as methyl or hydroxy(1-4C)alkyl, such as hydroxymethyl. R<sub>1b</sub> is preferably a hydrogen atom. The alpha atom (Y) is preferably a CH or C(CH<sub>3</sub>) group,  
20 especially CH.

Preferably, the group ~~Lp~~Lp(D)<sub>n</sub> is selected from the following formulae:

X



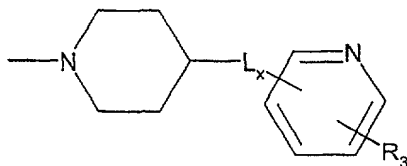




m represents 0 or 1; and

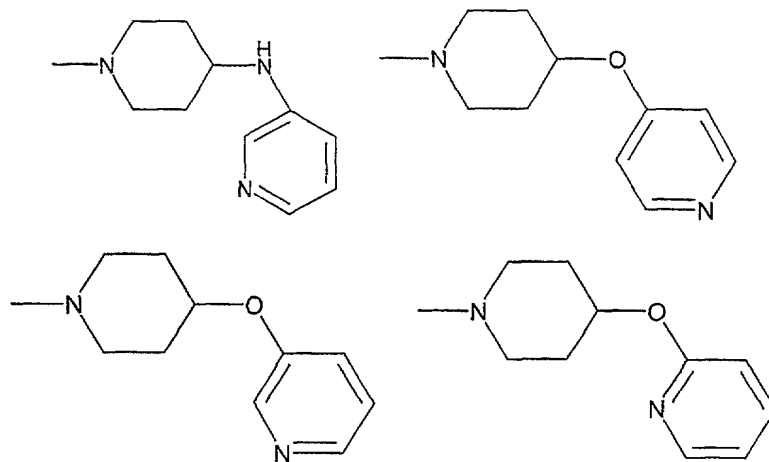
10 tetrazolyl.

X



in which  $L_x$  represents 0 or NH.

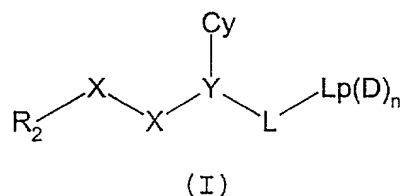
15 the following formulae:



Hard amended claims

## Claims

1. A serine protease inhibitor compound of formula (I)



wherein:

$\text{R}_2$  is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,  $\text{MeSO}_2$ - or  $\text{R}_1$ , or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or  $\text{R}_{1j}$ , and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxy, carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that  $\text{R}_2$  cannot be aminoisquinolyl;

each X independently is a C, N, O or S atom or a CO,  $\text{CR}_{1a}$ ,  $\text{C(R}_{1a})_2$  or  $\text{NR}_{1a}$  group, at least one X being C, CO,  $\text{CR}_{1a}$  or  $\text{C(R}_{1a})_2$ ;

each  $\text{R}_{1a}$  independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, carbonyl, alkylaminocarbonyl, alkoxy, carbonyl, amino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$\text{R}_1$  is as defined for  $\text{R}_{1a}$ , provided that  $\text{R}_1$  is not unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R<sub>3a</sub> or R<sub>3i</sub>X<sub>i</sub>;

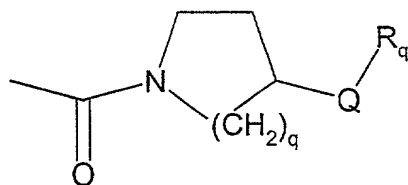
- 5 each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkylloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a  
 10 group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S; and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or -OCH<sub>2</sub>O- which is bonded to two adjacent  
 15 ring atoms in Cy;

X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub>;

R<sub>3i</sub> is phenyl, pyridyl or pyrimidinyl optionally substituted by R<sub>3a</sub>; and

R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>,

- 20 and -L-Lp(D)<sub>n</sub> is of the formula:



wherein:

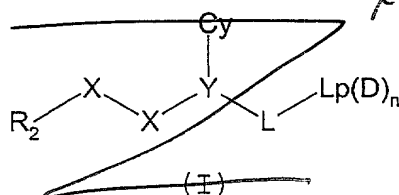
q is 1 or 2;

Q is -O- or -NH-;

- 25 and R<sub>q</sub> is R<sub>c</sub> which is pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl or phenyl (which phenyl or pyridyl group may bear a fluoro, chloro, alkyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, dialkylaminosulphonyl, methoxy, methylthio, alkylsulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino,  
 30 alkoxycarbonyl, acetyl amino, cyano, ethoxy, nitro, hydroxy,

alkylsulphonylamino, triazolyl or tetrazolyl substituent);  
or a physiologically-tolerable salt thereof.

(amended)  
2. A serine protease inhibitor compound of formula (I) <sup>according to claim 1</sup>



wherein:

R<sub>2</sub> is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub>- or R<sub>1</sub>, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R<sub>2</sub> cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR<sub>1a</sub>, C(R<sub>1a</sub>)<sub>2</sub> or NR<sub>1a</sub> group, at least one X being C, CO, CR<sub>1a</sub> or C(R<sub>1a</sub>)<sub>2</sub>;

each R<sub>1a</sub> independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R<sub>1</sub> is as defined for R<sub>1a</sub>, provided that R<sub>1</sub> is not

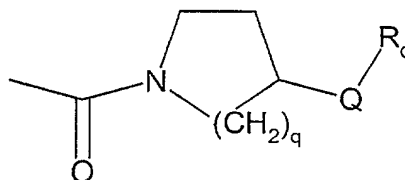
unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R<sub>3a</sub> or phenyl optionally substituted by R<sub>3a</sub>;

each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>, and -L-Lp(D)<sub>n</sub> is of the formula:



wherein:

q is 1 or 2;

Q is -O- or -NH-;

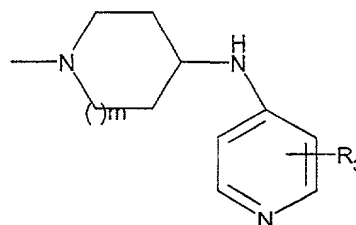
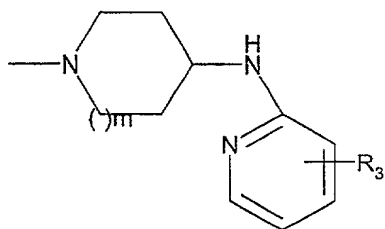
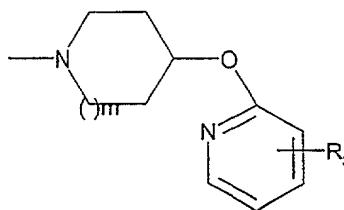
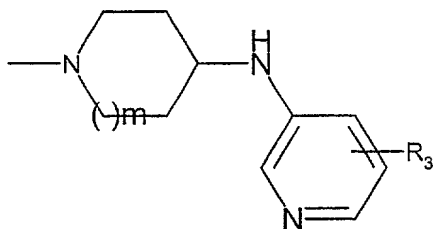
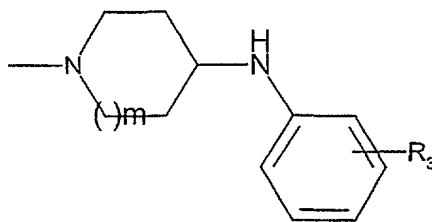
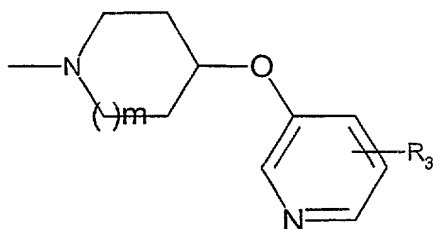
and R<sub>q</sub> is R<sub>c</sub> which is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent); or a physiologically-tolerable salt thereof.

(amended)

3. A compound according to ~~either~~ claim 1 ~~or claim~~ 2 wherein q is 2.

(amended)

4. A compound according to ~~any of claims 1 to 3~~ <sup>2</sup> wherein -Lp(D)<sub>n</sub> is selected from the following formulae:



5

wherein:

m represents 0 or 1; and

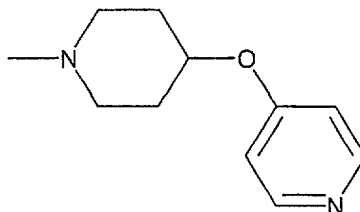
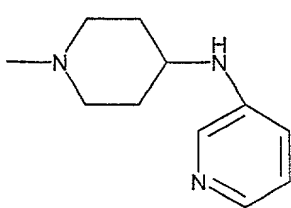
when R<sub>3</sub> is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl,

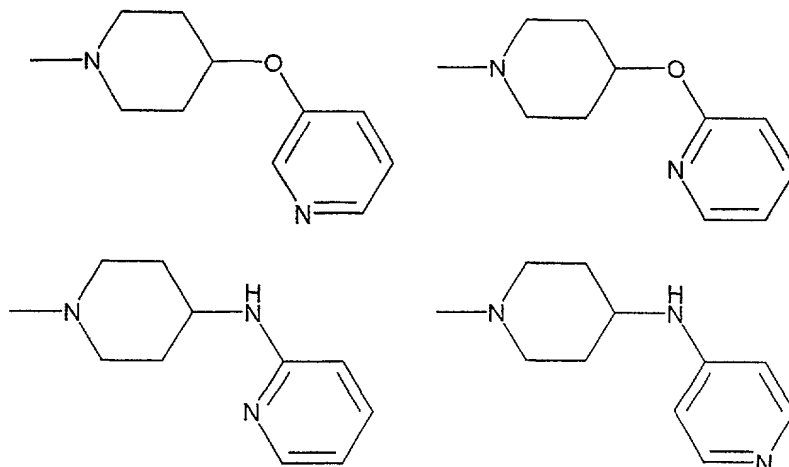
10 alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxy, acetyl, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

(amended)

2

15 5. A compound according to ~~any of claims 1 to 3~~ wherein - Lp(D)n is selected from the following formulae:





(amended)

6. A compound according to ~~any one of claims 1 to 5~~ wherein  
5 Q is -NH-.

(amended)

7. A compound according to ~~any of claims 1 to 3~~ wherein R<sub>c</sub>  
is pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazin-3-yl,  
pyridazin-4-yl, pyrimid-4-yl or phenyl.

(amended)

8. A compound according to ~~any of claims 1 to 3~~ wherein R<sub>c</sub>  
is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-  
methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-  
methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

(amended)

9. A compound according to ~~any one of claims 1 to 8~~ wherein  
R<sub>2</sub> is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl,  
benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl  
(each of which is optionally substituted as defined in claim

10 1).

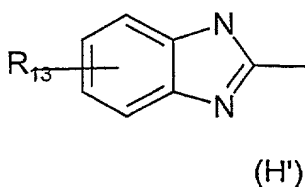
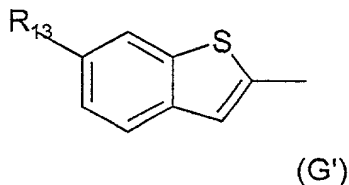
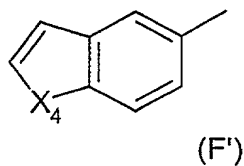
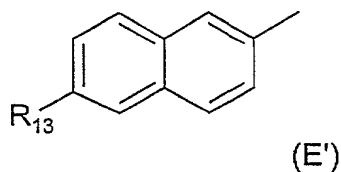
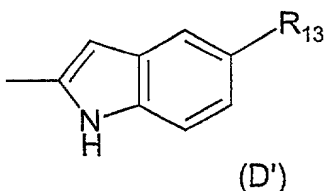
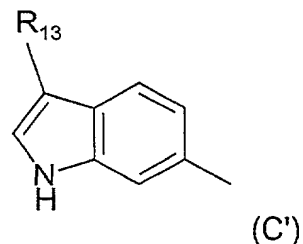
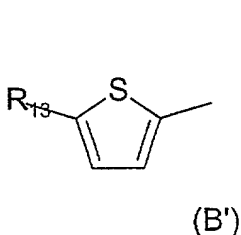
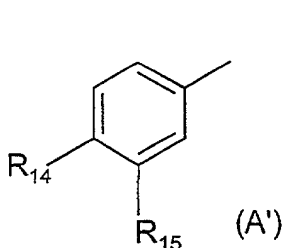
(amended)

10. A compound according to ~~any one of claims 1 to 9~~ wherein  
optional substituents for R<sub>2</sub> are selected from:  
fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy,  
25 trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano,  
trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino,

carboxy, acetoxy, hydroxy, methyl, ethyl, amido (CONH<sub>2</sub>), aminomethyl, methoxy and ethoxy.

(amended)

11. A compound according to ~~any one of claims 1 to 10~~ wherein  
 5 R<sub>2</sub> is selected from one of the formula (A') to (H'):



wherein X<sub>4</sub> is O or S, R<sub>13</sub> is selected from hydrogen, chloro or methyl and R<sub>14</sub> is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R<sub>15</sub> is selected from hydrogen, methyl, fluoro, chloro and amino.

12. A compound according to claim 11, wherein R<sub>2</sub> is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.



(amended)

13. A compound according to ~~any one of claims 1 to 12~~ wherein -X-X- is -CONH-.

5

(amended)

14. A compound according to ~~any one of claims 1 to 13~~ <sup>any one of claims 1 to 13, 15 to 16 and</sup> 14 to 22 wherein Y is CH.

(amended)

15. A compound according to ~~any one of claims 1 to 14~~  
 10 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl  
 15 or cycloalkyl group, or a phenyl group substituted by R<sub>3i</sub>X<sub>i</sub> in which X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub> and R<sub>3i</sub> is phenyl or pyridyl optionally substituted by R<sub>3a</sub>.

(amended)

2

16. A compound according to ~~any one of claims 1 to 14~~,  
 20 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

(cancelled on national phase entry)

17. ~~A compound according to any one of claims 1 to 16~~  
 25 wherein R<sub>3a</sub> is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl,  
 30 alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a

~~group of the formula  $C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S, and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and  $-OCH_2O-$  which is bonded to two adjacent ring atoms in Cy.~~

*(Cancelled on national phase entry)*

18. ~~A compound according to any one of claims 1 to 16 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, alkoxy, alkyl~~

10 ~~(optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl,~~

15 ~~alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.~~

20 *(amended)*

19. ~~A compound according to any one of claims 1 to 16 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl,~~

25 ~~ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,  $CONH_2$ ,  $CH_2CONH_2$ , acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl,~~

30 ~~methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and  $-OCH_2O-$  (which is bonded to two adjacent ring atoms in Cy).~~

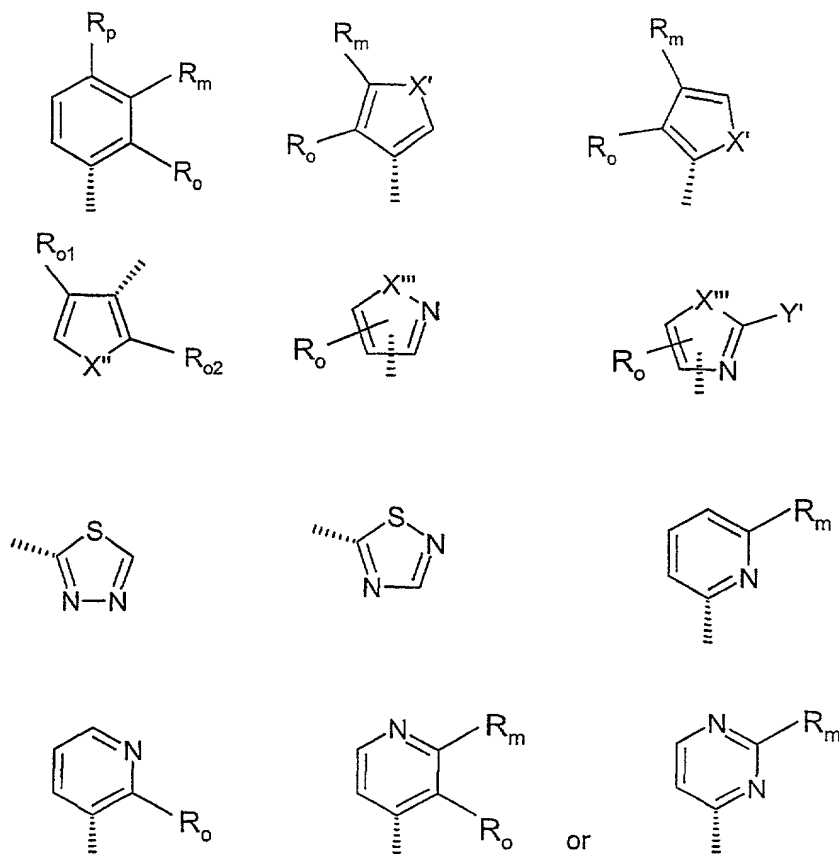
(amended)

2

20. A compound according to ~~any one of claims 1 to 16~~ wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,  $\text{CONH}_2$ ,  $\text{CH}_2\text{CONH}_2$ , acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

(amended)

- 15 21. A compound according to ~~any one of claims 1 to 16~~ wherein Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

5 X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R<sub>O</sub> is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl and methylsulphonyl;

10 R<sub>m</sub> is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S, and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl or ethyl or  
15 together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);  
R<sub>p</sub> is selected from hydrogen and fluoro; or  
R<sub>O</sub> and R<sub>m</sub> or R<sub>m</sub> and R<sub>p</sub> form an -OCH<sub>2</sub>O- group; or  
R<sub>O</sub> and R<sub>m</sub> together with the ring to which they are attached  
20 form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and  
one of R<sub>O1</sub> and R<sub>O2</sub> is hydrogen and the other is R<sub>O</sub>.

(amended)

25 22. A compound according to ~~any one of claims 1 to 16~~ wherein  
Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-  
30 yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

23. A compound as claimed in Claim 1, which is selected from 1-(indol-6-carbonyl-D-phenylglyciny)-4-(4-pyridoxy)-

piperidine; 1-[indole-6-carbonyl-D,L-(2-chlorophenyl)glycinyll]-4-(pyridin-4-yloxy)piperidine, and physiologically-tolerable salts thereof.

(amended)

14

- 5 24. A compound as claimed in ~~any one of Claims 1 to 23~~, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $\text{NH}_2\text{-CR}_{1b}(\text{Cy})\text{-COOH}$  where the  $\text{NH}_2$  represents part of X-X.

(amended)

- 10 25. A pharmaceutical composition, which comprises a compound as claimed in ~~any one of Claims 1 to 24~~ together with at least one pharmaceutically acceptable carrier or excipient.

(cancelled on national phase entry)

- 15 26. A compound as claimed in any one of Claims 1 to 24 for use in therapy.

(cancelled on national phase entry)

27. ~~Use of a serine protease inhibitor according to any one of Claims 1 to 24 for the manufacture of a medicament for the treatment of a thrombotic disorder.~~

20 (cancelled on national phase entry)

28. ~~A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 24 together with at least one pharmaceutically acceptable carrier or excipient for use in the treatment of a thrombotic disorder.~~

25

29. A method of treatment of the human or non-human animal body to combat a thrombotic disorder, said method comprising administering to said body an effective amount of a compound according to Claim 1.

30 (cancelled on national phase entry)

30. ~~A compound of formula I as claimed in Claim 1 and named in any one of the Examples herein, or a physiologically acceptable salt thereof.~~

Add new claim 31 to 35